Acetoacetate/β-hydroxybutyrate Ratio in Arterial Blood and Liver during and after Liver Ischemia : A Clue to Detect the Viability of Ischemic Liver

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Arch Jpn Chir 52(4), 508～519, Juli, 1983

Acetoacetate/β-hydroxybutyrate Ratio in Arterial Blood and Liver during and after Liver Ischemia —A Clue to Detect the Viability of Ischemic Liver—

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Received for Publication, April 8, 1983.

Summary

Prognosis of animals after liver ischemia (LI) depends on mitochondrial phosphorylative activity of the liver. However, it is still difficult to assay mitochondrial activities clinically. In the present study, varying periods (15, 30, and 60 min) of normothermic ischemia of the total liver followed by restoration of blood flow were studied on Wistar rats, in order to evaluate the value of ketone body ratio (acetoacetate/β-hydroxybutyrate) in arterial blood for detection of viability of ischemic liver. Ketone body ratio in arterial blood well reflects the ketone body ratio in liver (the oxidoreduction state in mitochondria) and the hepatic energy charge. The tendency of recovery after restoration of blood flow was indicative for prognosis.

Introduction

Temporary occlusion of the hepatic artery and portal vein in order to accomplish appropriate hemostasis of the liver is a necessary technique during operations for radical extirpation of liver tumor, isolated perfusion chemotherapy against hepatic cancer, treatment for major hepatic trauma or liver transplantation.

Experimental and clinical studies have revealed a rather limited tolerance of the liver to ischemia[2,4]. Hepatic cell necrosis due to ischemia[2,4,9,12,14,24,26] and other hepatic or extrahepatic factors such as activities of the reticuloendothelial system[15], hepatic outflow block syndrome[23], release of vasoactive substances[16] including endotoxin[5], lethal effects of portal pooling of blood[11], and hyperkalaemia[6] have been intensively studied as possible causes of death.

It has been particularly indicated that the viability of liver or the prognosis of animals after liver ischemia depends on mitochondrial phosphorylative activities in the liver[8,12,28]. However, it is still difficult to assay the mitochondrial activity for clinical purposes.

Key words: Liver ischemia, Ketone body ratio, Energy charge, Oxidoreduction state.
索引語：阻血肝，ケトン体比，エネルギーチャージ，酸化還元状態.
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In a previous work[27], it was reported that the acetoacetate/β-hydroxybutyrate ratio (AcAc/β-BOH) in arterial blood correlated both with the ratio in liver and the hepatic energy charge (EC), (ATP+1/2 ADP)/(ATP+ADP+AMP), a parameter of intracellular energy status[1]. The ratio in liver represents the ratio between oxidized and reduced forms of free nicotinamideadenine dinucleotides (NAD^+/NADH ratio) in the mitochondrial compartment of liver[29].

These ketone bodies are produced only in the liver; they are not oxidized in the liver, but delivered to peripheral tissues[19]. The concentration of ketone bodies in blood represents the balance between their production by liver and their utilization by peripheral tissues. Therefore, the analysis of ketone bodies in arterial blood is more informative with respect to liver alterations than measurements in peripheral venous blood.

In this study an effort has been made to determine a relationship between ketone body ratios in liver and arterial blood during and after LI. The ketone body ratios are further compared with the hepatic energy charge and pyruvate/lactate ratio which reflects the oxidoreduction state in cytoplasmic compartment of liver[29].

Materials and Methods

Male Wistar rats weighing 200–250 g were maintained on a balanced laboratory chow and water *ad libitum* 1 week before treatment. Food was withdrawn 15 hours before the experiments. The rats were anesthetized with an intraperitoneal injection of 25 mg of pentobarbital sodium per kg body weight and fixed on a surgical board in a supine position. A midline laparotomy was performed. About 30 to 60 min after the injection of pentobarbital sodium, when anesthesia became lighter and some reflexes returned, LI was induced by clamping the entire gastrohepatic ligament including the hepatic artery, the portal vein and the common bile duct. About 10 mg/kg of pentobarbital sodium was readministrated intraperitoneally, if necessary at least 30 min before the specimen sampling.

The experiments were performed in four groups. In group 1, the mean arterial blood pressure (MABP) was measured before, during and after LI of varying duration. A teflon tube of 0.8 mm inner diameter was inserted into the abdominal aorta via the left femoral artery; after administration of 500 units of heparin, it was connected with a Statham strain gauge and a Hellige monitor. In group 2, about 1 g of the left lateral lobe of liver was sampled by means of the Wollenberger freeze-stop-technique[30], in order to assay metabolites in liver under varying experimental conditions: a) controls sampled 30–60 min after induction of anesthesia, b) data from rats 1 hour after sham-operation consisting of the separation of the gastro hepatic ligament without ligation, and c) data at various points of time during and after LI. In group 3, metabolites were measured in the arterial blood under the same conditions like in group 2. About 1 ml blood was withdrawn without sucking from the abdominal aorta into a syringe containing 1 ml 10%(w/w) ice-cold perchloric acid. Specimens on the 5th day after restoration of hepatic blood flow were sampled in the same manner as in control rats. In group 4, specimens of liver tissue and arterial blood were sampled simultaneously, in order to control and ascertain the results in group 2 and 3 and to correlate the ketone body ratio in arterial blood to that in the

liver and the hepatic energy charge. The left lateral lobe was frozen between pre-cooled tongs[30], the remaining liver lobes were clamped with curved forceps for hemostasis without pulling liver downward, the frozen liver lobe was severed and both the tissue and tongs were transferred into liquid oxygen. Immediately thereafter, blood was withdrawn from the abdominal aorta.

Tissue specimens and blood samples were prepared and extracted as previously described[27]. Concentrations of acetoacetate (AcAc), β-hydroxybutyrate (β-BOH), pyruvate, lactate, ATP, ADP, and AMP were measured enzymatically with approved methods[7]. The energy charge[1] was calculated as (ATP+1/2 ADP)/(ATP+ADP+AMP).

All results are expressed as mean±SEM. The significance between means was determined by Student's t-test.

Results

The changes in the metabolic pattern of liver in group 2 and arterial blood in group 3 during and after LI of 15 or 30 min duration were identical with those in group 4. However, in group 4 it was found methodically insufficient to obtain liver and blood samples simultaneously after 60 min LI. Data on 60 min LI without and with resumption of liver perfusion refer to groups 2 and 3 only, while all other metabolic data were obtained from group 2 to 4. The correlations between metabolic changes in liver and blood were solely derived from group 4 experiments.

Mortality: There were no deaths either in control and sham-operated rats or in rats submitted to up to 15 min of LI without and with resumption of liver circulation. During recovery from 30 min LI, two of six rats (33%) in group 1 and 21 of 58 animals (36%) in group 2 to 4 died within 60 min. In experiments designed for a 5 days' follow-up in groups 2 and 3, four of 12 rats (24%) expired 50 to 60 min after induction of LI. Upon restoration of blood flow after 60 min LI, all rats (4 in group 1, 13 in group 2 and 3) died within 30 min.

Blood Pressure: MABP (group 1, Fig. 1) averaged under control conditions 111 torr. Upon induction of LI, it decreased drastically to 55 and 39 torr within 7 and 15 min respectively.

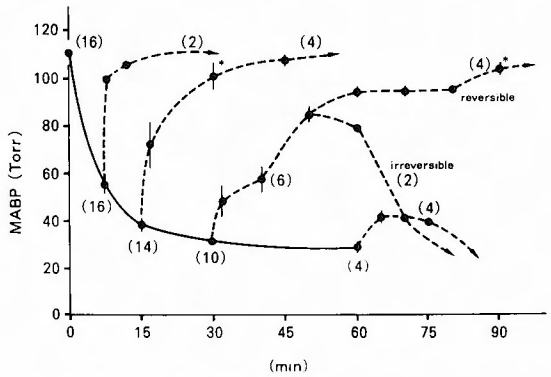

Fig. 1. MABP (x±SEM) during liver ischemia (——) and upon restoration of liver blood flow after 7, 15, 30, and 60 minutes of liver ischemia (----) respectively. Number of experiments in brackets.
*not significantly different from control before liver ischemia

After 60 min, it averaged 29 torr. Restoration of liver circulation after 15 min LI resulted in a normal MABP within 15 min. After 30 min LI, the control range was reached within 60 min in surviving rats. MABP decreased continuously after an initial recovery in irreversibly damaged animals. After 60 min LI, MABP only recovered poorly and transitorily.

Adenine Nucleotides (AN): The tissue levels of AN in the liver (Fig. 2) were identical in control and sham-operated rats. LI resulted in a significant decrease in ATP ($p<0.001$) and total AN ($p<0.01$) and a significant increase in AMP ($p<0.001$) within 15 min, while ADP did not change. The total AN (TAN) decreased further ($p<0.01$) with prolonged LI. Restoration of blood flow after 15 min LI returned the tissue levels of AN to normal ranges within 15 min. Rats surviving a LI of 30 minutes' duration also exhibited a definite but retarded recovery of AN upon restoration of the liver circulation, and the values had reached the control range within 5 days. In rats which died after LI of 30 minutes' duration, the liver AN did not show any significant change in comparison to the values at the end of LI. The same was true for livers of rats after 60 min LI.

Ketone Bodies in Liver and Blood: The liver tissue levels and the concentrations in arterial blood of the ketone bodies AcAc and β-BOH (Fig. 3) exhibited considerable individual variations under the various experimental conditions. In spite of that, some alterations were very distinct. The alteration from control to sham-operated rats resulted in significant increases ($p<0.05$) in liver AcAc and β-BOH, while the blood levels of these ketone bodies were not significantly affected. During LI, AcAc in liver and arterial blood exhibited a drastic decrease within 15 min

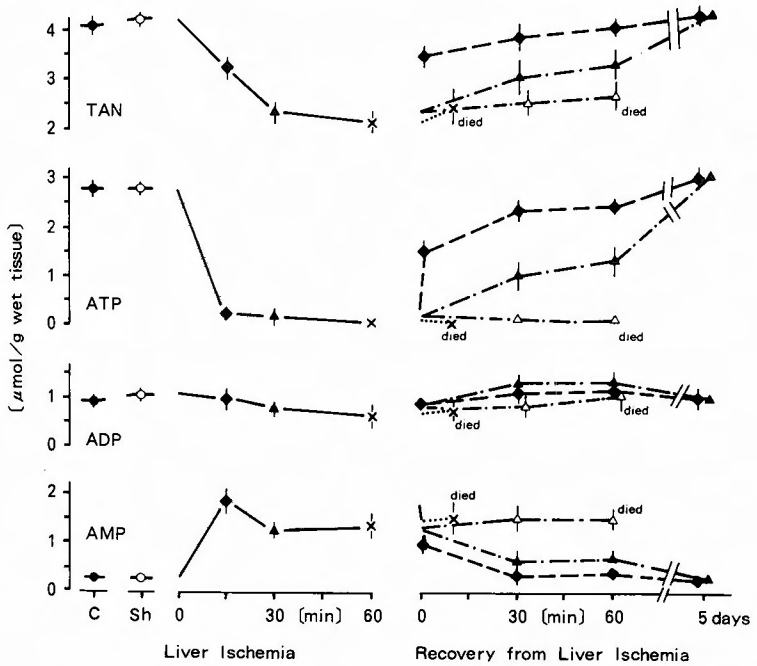

Fig. 2. ATP, ADP, AMP and total adenine nucleotides (TAN) (μ mol/g wet liver) of control (C) or sham-operated (Sh) rats and of rats surrendered to liver ischemia without and with reperfusion (for n see Table 1, x±SEM).

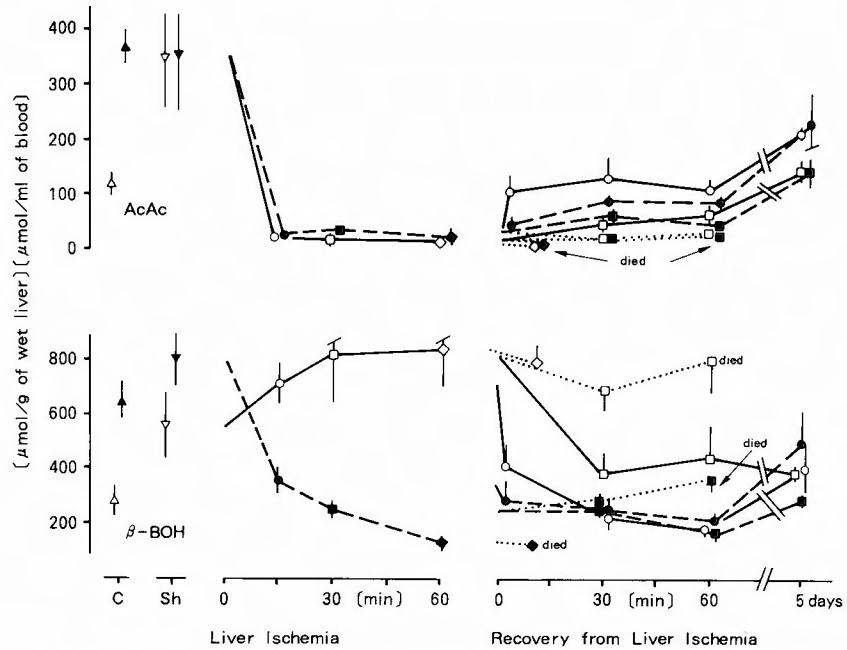

Fig. 3. AcAc and β-BOH in the liver (μ mol/g wet liver) and arterial blood (μ mol/ml) of control (C) or sham-operated (Sh) rats and of rats surrendered to liver ischemia without and with reperfusion (for n see Table 1, x±SEM).
Open symbols, solid lines: Liver
Filled symbols, dashed lines: Blood
Symbols and dotted lines: Animals died during recovery from liver ischemia.

both in comparison to the results in control and sham-operated animals ($p<0.001$). β-BOH in liver increased significantly during LI in relation to the control ($p<0.001$). The arterial blood concentration of β-BOH, however, already decreased significantly after 15 min LI ($p<0.01$) and continued to decrease during the consecutive 45 min ($p<0.01$). Restitution of blood flow after 15 min LI resulted in a prompt increase in AcAc ($p<0.05$) and decrease in β-BOH ($p<0.001$) in the liver. At 5 days, they reached the lower range found in sham-operated animals. The LI-induced significant reduction in the blood concentartions was slowly compensated within 5 days, if the values were compared with those in sham-operated animals. In rats, the liver of which was rendered ischemic for 30 min and which survived, the tissue level of AcAc continually rose ($p>0.05$ at 30 min of recovery), while liver β-BOH tended to decrease. After 5 days, the tissue levels of ketone bodies tended to be higher than the control levels but lower than the levels in the sham-operated group. The changes in the blood concentrations largely paralleled those in the liver. AcAc and β-BOH in liver and blood did not change post-ischemically in rats which did not survive 30 min LI and in rats surrendered to 60 min LI.

Lactate and Pyruvate in Liver and Blood: Lactate and pyruvate tissue levels and arterial blood concentrations (Fig. 4) were not significantly different in control and sham-operated rats. In the ischemic liver, lactate accumulated significantly ($p>0.001$ at 30 min), while pyruvate decreased ($p<0.05$ at 60 min). Blood lactate and pyruvate increased continuously during

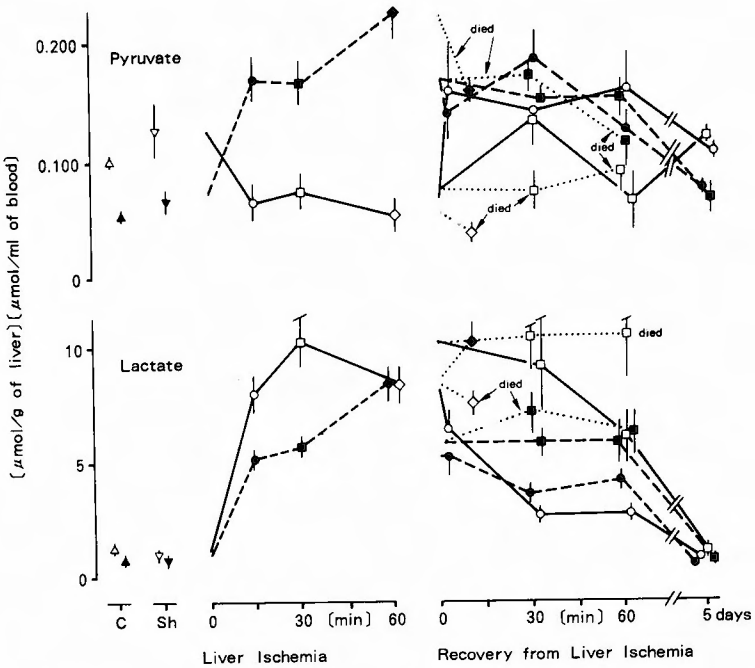

Fig. 4. Pyruvate and lactate in the liver (μ mol/g wet liver) and arterial blood (μ mol/ml) of control (C) or sham-oeprated (Sh) rats and of rats surrendered to liver ischemia without and with reperfusion (for n see Table 1, x±SEM).
Open symbols, solid lines: Liver
Filled symbols, dashed lines: Blood
Symbols and dotted lines: Animals died during recovery from liver ischemia.

the period of LI; the increases were significant already after 15 min ($p<0.001$ for lactate, $p<0.01$ for pyruvate). Upon resumption of liver perfusion after 15 and 30 min LI, lactate started to decline in the liver tissue and the blood. Recovery was slower with prolonged periods of LI. At 60 min of recovery, the values were still significantly elevated ($p<0.01$ at least). At 5 days, the tissue levels and blood concentrations were within the control levels. In rats which did not recover from 30 min LI or which had been surrendered to 60 min LI, there were no significant changes in liver tissue or blood in comparison to the values found at the end of the period of LI. During the first hour of recovery from 15 or 30 min LI, the liver tissue level of pyruvate readily increased, while the elevated blood concentrations of pyruvate exhibited little changes. Animals which did not recover from 30 min LI or had 60 min LI showed no post-ischemic increase in liver pyruvate. At 5 days, the tissue levels and blood concentrations were within the control ranges.

Metabolic Ratios: EC in liver, the ratio AcAc/β-BOH in liver and arterial blood, and the ratio pyruvate/lactate in blood (Fig. 5) were not significantly different in control and sham-operated rats. The pyruvate/lactate ratio in liver increased ($p<0.05$) in sham-operated animals in comparison to the controls. Induction of LI altered the metabolic ratios in the same direction. Within 15 min, EC decreased from 0.80 to 0.26 ($p<0.001$), the ratio AcAc/β-BOH in liver and blood dropped from mean values between 0.45 and 0.65 to values below 0.08 ($p<0.001$), and the ratio pyruvate/lactate decreased from 7.71 in liver and from 6.74 in blood of control rats to

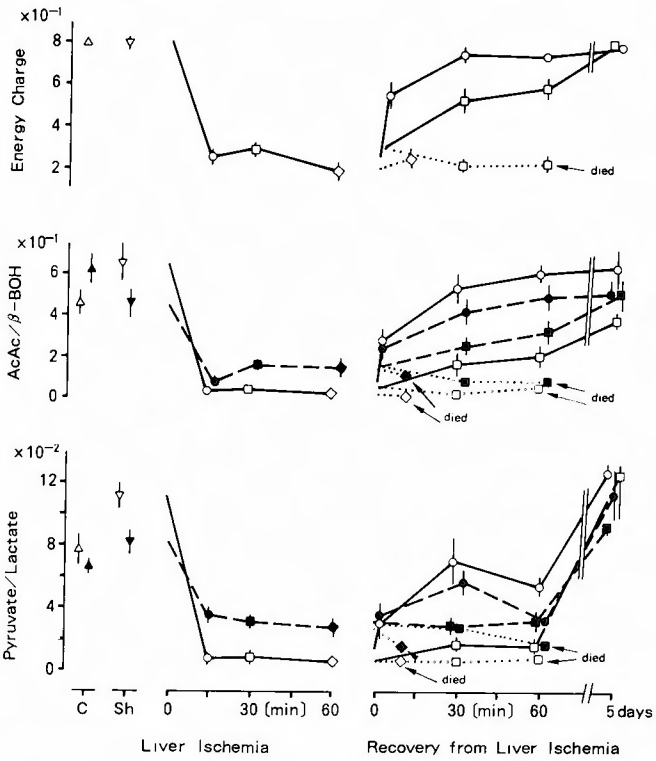

Fig. 5. The energy charge, AcAc/β-BOH, and pyruvate/lactate of control (C) or sham-operated (Sh) rats and of rats surrendered to liver ischemia without and with reperfusion (for n see Table 1. x±SEM).
Open symbols, solid lines: Liver
Filled symbols, dashed lines: Blood
Symbols and dotted lines: Animals died during recovery from liver ischemia.

0.88 ($p<0.001$) and 3.62 ($p<0.001$) respectively. During the further course of LI, there were minor changes only. When LI was suspended, there were no changes in the liver and the arterial blood of those animals which did not recover from 30 min LI or which had undergone

Table 1. Survey of numbers of animals used in the experiments depicted in Fig. 2, 3 and 4 for analysis of adenine nucleotides in liver tissue/ketone bodies, lactate and pyruvate in liver tissue/ketone bodies, lactate and pyruvate in arterial blood.

Duration of Liver Ischemia	Recovery from Liver Ischemia					
	None	3 min	10 min	30 min	60 min	5 days
15 min	10/10/13	11/11/10		9/11/12	5/ 7/12	5/ 5/ 5
30 min	11/10/11					
reversible				6/ 6/ 6	6/ 6/ 6	5/ 5/ 5
irreversible				6/ 6/ 6	7/ 7/ 7	
60 min	5/ 5/ 6		5/ 5/ 6			
Controls	7/ 7/12					
Sham-Operations	5/ 5/ 6					

Table 2. Correlations between metabolic data in liver tissue and arterial blood during and after LI of 15 or 30 minutes' duration.

Correlation between	n	Correlation equation	r=	p<
AcAc/β-BOH in liver (x) Hepatic EC (y)	33	y=0.857 x+0.302	0.872	0.001
AcAc/β-BOH in arterial blood (x) AcAc/β-BOH in liver (y)	33	y=1.050 x−0.012	0.835	0.001
AcAc/β-BOH in arterial blood (x) Hepatic EC (y)	33	y=0.986 x+0.263	0.794	0.001
Pyruvate/Lactate in arterial blood (x) Hepatic EC (x)	33	y=0.031 x+0.354	0.681	0.001

60 min LI. During recovery from 15 min LI, there was a significant increase in EC ($p<0.001$), AcAc/β-BOH ratio ($p<0.001$) and pyruvate/lactate ratio ($p<0.05$) of the liver tissue as well as in the ratio AcAc/β-BOH in blood within 3 min. The control ranges were reached within 30 min. The pyruvate/lactate ratio recovered more slowly, but was normal within 5 days. Rats surviving 30 min LI exhibited a retarded recovery of metabolite ratios in comparison to 15 min LI. There was an increase in EC to 0.54 ($p<0.01$) and 0.60 ($p<0.001$), in the ratio AcAc/β-BOH of the liver to 0.17 ($p<0.05$) and 0.22 ($p<0.01$) and in the blood to 0.26 (n.s.) and 0.34 ($p<0.05$) respectively after 30 and 60 min recovery, while the changes in the pyruvate/lactate ratio of liver and blood were negligible. At 5 days, all metabolite ratios under investigation were within the ranges found in control or sham-operated rats.

Correlation Coefficients: There were very close linear correlations between the metabolic

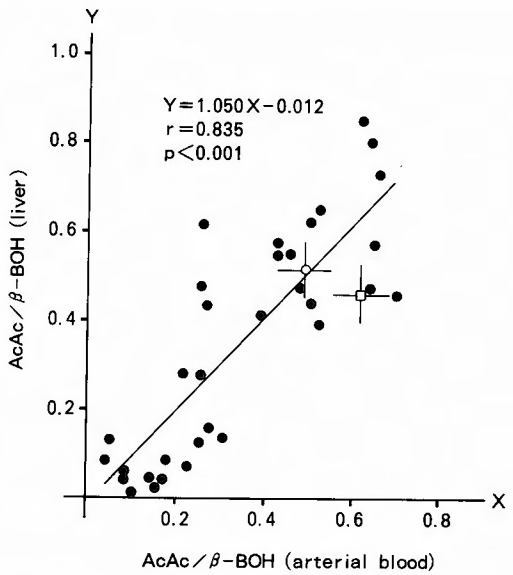

Fig. 6. Relationship between the ketone body ratio in arterial blood (X) and in liver (y) during and after 15 and 30 min LI.
○ sham-operated rats (mean±SEM)
□ control rats (mean±SEM)

alterations in liver and arterial blood during and after LI of 15 or 30 min duration, which are summarized in Table 2 and Figure 6.

Discussion

Survival of animals after LI is a function of the duration of LI. Metabolic disorders which determine the animals' life during and after LI may be devided into hepatic and extrahepatic factors. The most important factor is the necrotic change of liver due to anoxia. Prolonged LI is characterized by mitochondrial swelling and the dilatation and fragmentation of the endoplasmic reticulum[4]. The cells progress from a stage of reversible alterations to a stage of irreversible alterations. Decreased supplies of glucose[20] and ketone bodies to peripheral tissues lead to finally irreversible changes in peripheral organs[25]. The extrahepatic factors resulting from LI become metabolic loads on the damaged liver after resumption of hepatic blood flow. E.g., interruption of hepatic blood flow inhibits the Cori cycle and induces lactacidosis[3]. The inhibition of the urea cycle results in hyperammonemia[17]. Upon restoration of blood flow, ATP demands in the damaged liver for gluconeogenesis and detoxication processes are not negligible and deteriorate the intracellular energy balance[17].

Although there are numerous events taking place after recirculation of blood, the viability of liver can be considered to depend on the balance between the capacity of ATP synthesis in mitochondria and the extent of accumulated metabolic loads. If the damaged mitochondria can not compensate energy demands to sustain intracellular energy levels in normal limits, the metabolic disorders in liver together with those in peripheral tissues lead to the animals' death. After interruption of blood flow, EC and oxidoreduction states in liver mitochondria and cytoplasm decreased to very low levels within 15 min. It is apparent that after depletion of energy stores in the early stage, liver mitochondria did not function to sustain the intracellular energy levels in normal limits due to anoxia and lack of substrates. However, completely different processes of recovery from LI of 15, 30 or 60 min imply that necrotic damages in liver during 15 min LI were relatively small and the intact mitochondria could produce energy immediately after recirculation, while damages at 1 hour became so intensive that mitochondria which had not been damaged irreversibly could not compensate incoming metabolic overloads. The pattern of recovery after 30 min LI indicates that the mitochondrial damages were critical and only those mitochondria which could overcome incoming energy demands during the first hour of recovery apparently were able to survive finally. It has been also certified by histological studies that the tolerance to ischemia of rat liver cells is limited to 30 to 45 min[2] or does not exceed 60 min[4].

In spite of the large individual scattering, AcAc and β-BOH exhibited a characteristic and reproducible change during and after LI. The change may indicate some biochemical aspects of liver ischemia relating with the oxidoreduction state[13,18], but significant changes of ketone bodies in sham-operated rats imply that the absolute tissue levels also reflect other metabolic factors, such as influences of anesthesia, and are less reliable than the ratio for determining the hepatic energy levels.

The pyruvate/lactate ratio in liver changed parallel to the AcAc/β-BOH ratio and the EC

during and after LI. Since the oxidoreduction state in cytosol is linked to that in mitochondria by the malate-aspartate shuttle mechanism[21], these results may be reasonable. However, pyruvate and lactate, different from ketone bodies, are produced not only in the liver but also in other tissues. Lactate accumulated in the peripheral tissues during the period of hypotension accompanying LI, can be washed into the circulation after restoration of blood pressure. Due to this fact, the pyruvate/lactate ratio or lactate in arterial blood after resumption of liver circulation might be not directly indicative for the intrahepatic energy status.

The question of the critical period of LI has been intensively studied. Such studies should pay attention to important anatomical differences between species such as the extent of sphincter in the hepatic vein[23], different portal supply inside the liver[10], different rate of portopetal shunt[22], etc. In rats, the sphincter is very poorly developed and hepatic venous drainage therefore could be better than in dogs, rabbits or human beings during afferent circulatory interruption. It is possible that blood retrogradely enters the liver via the hepatic veins to some extent during LI. That might be, at least in part, the explanation for the result that the ketone bodies in arterial blood did not disappear during LI and that the ratio varied between 15 and 30 min.

In the present study the ketone body ratio in arterial blood well correlated with the ratio in liver and with the hepatic energy charge. If the ketone body ratio in arterial blood is assayed repeatedly according to a certain time schedule, it may be possible not only to know the mitochondrial oxidoreduction state in situ, but also to detect the mitochondrial capacity from a tendency of the recovering pattern and the viability of animals.

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和文抄録

肝阻血中及び還血後の動脈血中及び肝中のアセト酢酸/β-ハイドロオキシ酪酸比
—肝阻血動物の viability を知る手段—

京都大学医学部第一外科
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肝血流遮断(15分，30分，60分)時，及び，血流再開後の肝のエネルギー状態の変化をウィスターラットにより観察した．阻血肝の reversibility は肝ミトコンドリア (Mt) の燐酸化能の可逆性に依存している．動脈血中ケトン体比 (acetoacetate/β-hydroxybutyrate ratio) は出血性ショック動物において，肝 Mt 分画の NAD^+/NADH 比，肝の energy charge (EC)=(ATP+1/2 ADP)/(ATP+ADP+AMP) と相関して変動するという事実より，阻血肝動物の予後を血中ケトン体比の変動を介して追跡した．血中ケトン体比は阻血肝動物においても，肝 Mt 分画の NAD^+/NADH 比，肝 EC とよく相関して変動し，予後不良例では阻血時に低下したケトン体比は還血後も回復しなかったが，生存例ではケトン体比の回復をみた．還血後のケトン体比の回復傾向の分析が予後判定に有用である事が示唆された．